Synthesis of Novel 2-Azabicyclo[2.2.0]- and [2.1.1]hexanols

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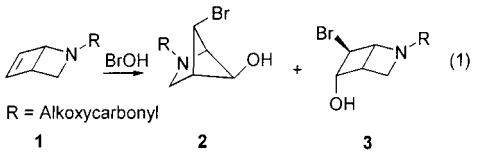
Methyl- and phenyl-substituted *N*-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes **6** were reacted with NBS in wet DMSO to afford bromohydrins. Mixtures of unrearranged 6-*exo*-bromo-5-*endo*-hydroxy-2-azabicyclo[2.2.0]hexanes **7a**,**b** and rearranged 5-*anti*-bromo-6-*anti*-hydroxy-2-azabicyclo-[2.1.1]hexanes **8a**,**b** were formed stereoselectively from the parent alkene **6a** and 4-methyl alkene **6b**. The 5-methyl alkene **6c** affords only unrearranged bromohydrin **7c** and dibromohydrin **9**. By contrast, solely rearranged 3-*endo*-substituted-2-azabicyclo[2.1.1]hexane bromohydrins **8d**−**f** result from additions to 3-*endo*-methyl alkene **6d**, 3-*endo*-4-dimethyl alkene **6e**, and 3-*endo*-phenyl alkene **6f**. As an alternative route to bromohydrins, the parent 5,6-*exo*-epoxide **10a** and 5-*endo*-methyl-5,6-*exo*-epoxide **10b** were ring opened with bromine/triphenylphosphine to afford unrearranged 5-*endo*-bromo-6-*exo*-hydroxy-2-azabicyclo[2.2.0]hexanes **11a**,**b**, while the 3-*endo*-methyl epoxide **10c** afforded solely the rearranged 5-*anti*-bromo-6-*anti*-hydroxy-3-*exo*-methyl-2-azabicyclo[2.1.1]hexane isomer **8g**. Tributyltin hydride reduction of bromohydrins **7a**,**b** and **11a** afforded novel 2-azabicyclo-[2.2.0]hexan-5-ols **13a**,**b** and -6-ol **14**, and bromohydrins **8a**,**b**, **8d**−**g** afforded new 2-azabicyclo-[2.1.1]-hexan-5-ols **15a**,**b** and **15d**−**g**.

Introduction

One strategy in the search for selective bioactive molecules is to constrain key pharmacophoric entities onto inflexible structures, such as fused or bridged small rings.[1] During our investigation of the hydroxybromination of *N*-(alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene **1** (eq 1),[2] it was discovered that rearranged 5-bromo-2-azabicyclo[2.1.1]hexan-6-ol **2** accompanied the 1,2-addition product 6-*exo*-bromo-2-azabicyclo[2.2.0]hexan-5-*endo*-ol **3**.[3,4] Both of these conformationally rigid bromohydrins possess halogen, amine, and alcohol functionalities amenable to further synthetic manipulations.[5] We were stimulated by the potential of this hydroxybromination rearrangement reaction for the generation of unique and potentially useful azabicyclohexanols[6] to expand the synthetic scope to substituted analogues of alkene **1**.[7]



Suitable substituted 2-azabicyclo[2.2.0]hex-5-enes **6** are available by established procedures (Scheme 1).[2,8,9] To investigate the effect upon the reaction course of an exo-

(1) For leading references, see: (a) Hart, B. P.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 2050. (b) Piotrowski, D. W. *Synlett* **1999**, 1091. (c) Esslinger, C. S.; Koch, H. P.; Kavanaugh, M. P.; Philips, D. P.; Chamberlin, A. R.; Thompson, C. M.; Bridges, R. *J. Bioorg. Med. Chem. Lett.* **1998**, *8*, 3101. (d) Koch, H. P.; Kavanaugh, M. P.; Esslinger, C. S.; Zerangue, N.; Humphrey, J. M.; Amara, S. G.; Chamberlin, A. R.; Bridges, R. *J. Mol. Pharmacol.* **1999**, *56*, 1095. (e) Mapelli, C.; van Halbeek, H.; Stammer, C. H. *Biopolymers* **1990**, *29*, 407. (f) Katagiri, N.; Yamatoya, Y.; Ishikura, M. *Tetrahedron Lett.* **1999**, *40*, 9069. (g) Bell, E. A.; Qureshi, M. Y.; Pryce, R. J.; Janzen, D. H.; Lemke, P.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 1409.

(2) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Christian, H.; Shaw, D. A.; Yuan, J. *J. Org. Chem.* **1998**, *63*, 8558.

(3) An isomeric bridged 6-*anti*-5-azabicyclo[2.1.1]hexane has been reported. Olivo, H. F.; Hemenway, M. S.; Gezginci, M. H. *Tetrahedron Lett.* **1998**, *39*, 1309.

(4) An *N*-alkyl-3-oxo lactam analogue of structure **3** has been reported. Begley, W. J.; Loe, G.; Cheetham, A. K.; Newsam, J. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2620.

(5) For use of an amino alcohol in a combinatorial library, see: Lohse, A.; Jensen, K. B.; Bols, M. *Tetrahedron Lett.* **1999**, *40*, 3033.

(6) For a review of synthetic approaches to isomeric 3-azabicyclo-[3.1.0]hexanes, see: Krow, G. R.; Cannon, K. C. *Org. Prep. Proced. Int.* **2000**, *32*, 103.

(7) Other synthetic routes to 2-azabicyclo[2.1.1]hexanols or to 3-substituted 2-azabicyclo[2.1.1]hexanes have not been reported. However, for synthesis of 2-azabicyclo[2.1.1]hexanes from substituted cyclobutylamines, see: (a) Stevens, C.; De Kimpe, N. *J. Org. Chem.* **1996**, *61*, 2174. (b) Gaoni, Y. *Org. Prep. Proced. Int.* **1995**, *27*, 185. (c) Park, T. H.; Ha, Y. H.; Jeong, D. Y. PCT Int. Appl. 1999; *Chem. Abstr.* **1999**, *130*, 182368. For photochemical ring closure of *N*-vinyl-*N*-allylamines to give C_1-, C_5-, and C_4-acyl-substituted 2-azabicyclo[2.1.1]-hexanes, see ref 1c−e and (d) Hughes, P.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 4793. (e) Hughes, P.; Martin, M.; Clardy, J. *Tetrahedron Lett.* **1980**, *21*, 4579. (f) Pirrung, M. C. *Tetrahedron Lett.* **1980**, *21*, 4577. (g) Tamura, Y.; Ishibashi, H.; Hirai, M.; Kita, Y.; Ikeda, M. *J. Org. Chem.* **1975**, *40*, 2702. (h) Ikeda, M.; Uchino, T.; Takahashi, M.; Ishibashi, H.; Tamura, Y.; Kido, M. *Chem. Pharm. Bull.* **1985**, *33*, 3279. (i) Swindell, C. S.; Patel, B. P.; deSolms, S. J.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 2346. (j) Schell, F. M.; Cook, P. M.; Hawkinson, S. W.; Cassady, R. E.; Thiessen, W. E. *J. Org. Chem.* **1979**, *44*, 1380. For photochemical ring closure of *N*-vinyl-*N*-allylamines to give C_1-aryl-substituted 2-azabicyclo[2.1.1]hexanes, see ref 1b. For synthesis of 2-aza-3-oxobicyclo[2.1.1]hexanes, see ref 7d and (k) Paquette, L. A.; Allen, G. R., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 4503.

(8) (a) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321. (b) Beecken, P.; Bonfiglio, J. N.; Hasan, I.; Piwinski, J. J.; Weinstein, B.; Zollo, K. A.; Fowler, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 6677. (c) Kurita, J.; Iwata, K.; Sakai, H.; Tsuchiya, T. *Chem. Pharm. Bull.* **1985**, *33*, 4572. (d) Kurita, J.; Iwata, K.; Tsuchiya, T. *Chem. Pharm. Bull.* **1987**, *35*, 3166. (e) Kurita, J.; Iwata, K.; Tsuchiya, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1188.

(9) See the accompanying manuscript: Krow, G. R. et al. *J. Org. Chem.* **2001**, *66*, 1805.

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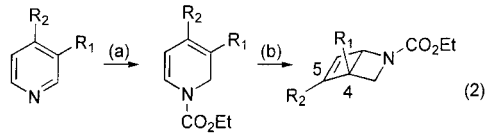
Scheme 1

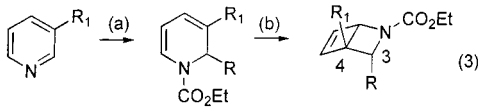


(2)

(a) $NaBH_4$, MeOH, ClCOOEt (b) photoirradiation

4a-c **5a-c** **6a-c**

a $R_1 = R_2 = H$
b $R_1 = CH_3$, $R_2 = H$
c $R_1 = H$, $R_2 = CH_3$



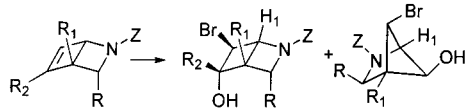
(3)

(a) MeMgBr or PhMgBr, (b) photoirradiation

4a-b **5d-f** **6d-f**

d $R = CH_3$, $R_1 = H$
e $R = R_1 = CH_3$
f R = Ph, $R_1 = H$

Table 1. Formation of Bromohydrins from 2-Azabicyclo[2.2.0]hex-5-enes 6



6 **7** **8**

$Z = CO_2Et$

		substituents				
entry	structure	R	R_1	R_2	products ratio	yield (%)
1	**6a**	H	H	H	**7a** + **8a** 7:3	70−80[a]
2	**6b**	H	CH_3	H	**7b** + **8b** 2:8	54
3	**6c**	H	H	CH_3	**7c** + **9**[b] 8:2	95
4	**6d**	CH_3	H	H	**8d**	85
5	**6e**	CH_3	CH_3	H	**8e**	60
6	**6f**	Ph	H	H	**8f**	47

[a] See ref 2. [b] Structure **9** is N-(ethoxycarbonyl)-5-*endo*-6-*exo*-dibromo-5-*exo*-hydroxymethyl-2-azabicyclo[2.2.0]hexane.

face alkyl group the azabicyclo[2.2.0]hex-5-ene **6b**, which has a methyl group at the C_4 bridgehead was chosen (eq 2). To determine the effect of a carbocation stabilizing substituent we chose the C_5-methyl substituted structure **6c** (eq 2). Structures **6d** and **6f**, in which there is either 3-*endo*-methyl- or 3-*endo*-phenyl substitution, enabled us to probe the influence of bottom face substituents, while 3-*endo*-4-dimethyl structure **6e** has the combined effects of methyl groups on both faces upon the reaction course. (eq 3).

Results and Discussion

Synthesis of 2-Azabicyclo[2.2.0]hex-5-enes 6 and Conversion to Bromohydrins. The requisite 2-azabicyclo[2.2.0]hex-5-enes **6b**−**f** (Scheme 1) were reacted with NBS in wet DMSO to afford substituent dependent mixtures of bromohydrins. The results are summarized in Table 1. The parent alkene **6a** (entry 1) has previously been reported by us to afford 7:3 mixtures of mainly 6-*exo*-bromo-5-*endo*-hydroxy-2-azabicyclo[2.2.0]hexane **7a** and minor amounts of rearranged 5-*anti*-bromo-6-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane **8a**.[2] The stereochemical assignment to the unrearranged bromohydrin **7a** was based upon ^1H NMR coupling constants. Absence of coupling between the bridgehead H_1 and H_{6endo} protons, consistent with a nearly 90° dihedral relationship between these two hydrogens, places the 6-bromine exo. The small coupling, $J_{5,6} = 4.2$ Hz, consistent with a trans relationship between H_5 and H_6, places the 5-hydroxyl group endo. These proton−proton coupling relationships facilitated the assignment of 6-*exo*-bromo-5-*endo*-hydroxy stereochemistry to the other unrearranged bromohydrins **7b**,**c**.

The stereochemical assignment to the rearranged bromohydrin **8a** (entry 1) was determined by the absence of vicinal coupling of the bridge protons H_5/H_6 with the adjacent bridgehead protons H_1/H_4. This is consistent with dihedral angles close to 90° and requires anti orientations for both the bromine and hydroxyl groups relative to the nitrogen containing bridge. Additionally, W-plan coupling $J_{1,4} = 7.2$ Hz and $J_{5,6} = 7.5$ Hz was exhibited. These coupling relationships facilitated the assignment of 5-*anti*-bromo-6-*anti*-hydroxy stereochemistry to the other rearranged bromohydrins **8b** and **8d**−**f**.

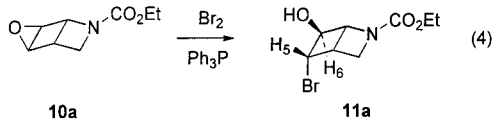
Addition of HOBr to 4-methyl-azabicycloalkene **6b** (entry 2) again afforded a mixture of bromohydrins. The unrearranged 4-methyl-bromohydrin **7b** exhibited a singlet for H_1 at δ 4.37; the absence of coupling with H_6 is consistent with an exo orientation for the 6-bromo substituent. Unfortunate overlap at δ 4.13 of the H_5/H_6 resonances precluded assignment of the hydroxyl stereochemistry as 5-endo until subsequent reductive removal of the bromine substituent (see alcohol **15b**, below). The rearranged bromohydrin **8b** exhibited a singlet for H_1 at δ 4.36; the absence of vicinal coupling for H_1 with either H_5 or H_6 is consistent with 5-*anti*-bromo-6-*anti*-hydroxy stereochemistry.

HOBr addition to the 5-methyl-azabicycloalkene **6c** (entry 3) afforded a mixture of unrearranged bromohydrin **7c** and dibromohydrin **9**. Neither the 5-methyl-bromohydrin **7c** nor the dibromohydrin **9** exhibited coupling between the *endo*-H_6 proton and H_1, consistent with 6-*exo*-bromine orientations. The 5-*exo* orientation of the methyl group of **7c** was based upon an observed NOE between H_4 and the 5-methyl, H_1, and H_{3exo} protons. The hydroxyl proton in dibromohydrin **9** is coupled to the adjacent geminal hydrogens ($J = 6.6$ Hz) indicative of a hydroxymethylene group. The absence of an NOE between the hydroxymethylene group and H_{6n}, and an observed NOE between H_4 and the methylene hydrogens (9%), is consistent with 5-*exo*-hydroxymethylene stereochemistry.

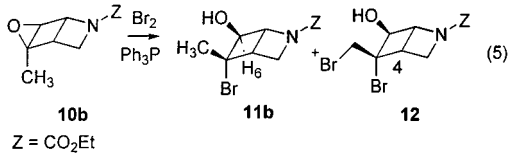
Addition of HOBr to the 3-*endo*-alkyl substituted azabicycloalkenes **6d**−**f** afforded solely rearranged bromohydrins of 5-*anti*-bromo-6-*anti*-hydroxy stereochemistry. The 3-*endo*-methyl bromohydrin **8d** (entry 4) and 3-*endo*-phenyl bromohydrin **8f** (entry 6), which have the methyl and phenyl groups syn to the bridge with the larger bromo substituent, had the usual W-plan couplings, $J_{1,4} = 7.5$ (7.2) Hz and $J_{5,6} = 7.5$ (7.5) Hz. The 3-*endo*-4-dimethyl bromohydrin **8e** (Entry 5) exhibited $J_{5,6} = 7.5$ Hz with H_1 appearing as a singlet at δ 4.38 in the absence of vicinal coupling.

Epoxidation of 2-Azabicyclo[2.2.0]hex-5-enes 6 and Conversion of Epoxides 10 to Bromohydrins. The epoxides **10a**−**c** were prepared by reaction of the 2-azabicyclo[2.2.0]hex-5-enes **6a** and **6c**,**d** with MCPBA in 75−80% yields as described by Tsuchiya.[8c] Addition of the epoxides **10** to a CH_2Cl_2 solution of bromine/

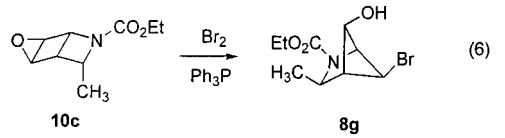
triphenylphosphine resulted in ring opening to afford bromohydrins.[10] The reaction of the parent epoxide **10a** (eq 4) afforded in 67% yield a bromohydrin assigned as 5-*endo*-bromo-6-*exo*-hydroxy-2-azabicyclo[2.2.0]hexane **11a** on the basis of the aforementioned absence of coupling between proton H_1 and the endo-H_6 and the trans coupling between protons H_5 and H_6 ($J_{5,6}$ = 5.4 Hz).



The 5-methyl epoxide **10b** afforded a mixture of bromohydrin **11b** (20%) and dibromo alcohol **12** (14%) (eq 5). Bromohydrin **11b** can also be assigned 5-*endo*-bromo-6-*exo*-hydroxy stereochemistry; absence of coupling between H_6 and H_1 is consistent with H_6 being endo. The 5-*endo*-bromo orientation is based on an observed NOE (7%) between the 5-methyl group and H_4. Dibromo alcohol **12** has a 6-*exo*-hydroxyl; there is a doublet at δ 4.88 for proton H_6 due to a coupling of 5.1 Hz with the hydroxyl proton, but proton H_1 at δ 4.46 (d) was coupled only to H_4 (J = 4.8 Hz). The 5-*endo*-bromo stereochemistry was assigned from the absence of an observed NOE between the bromomethylene and endo-H_6 and an observed NOE (6%) between the bromomethylene group and H_4.



The 3-*endo*-methyl epoxide **10c** afforded solely the rearranged bromohydrin **8g** (eq 6). The 5-*anti*-bromo-6-*anti*-hydroxy stereochemistry of **8g** can be assigned on the basis of the W-plan couplings $J_{1,4} = J_{5,6}$ = 7.2 Hz, and the absence of observed vicinal couplings $J_{1,5} = J_{1,6} = J_{3,4} = J_{4,5} = J_{4,6} = 0$. The 3-*exo*-methyl stereochemistry

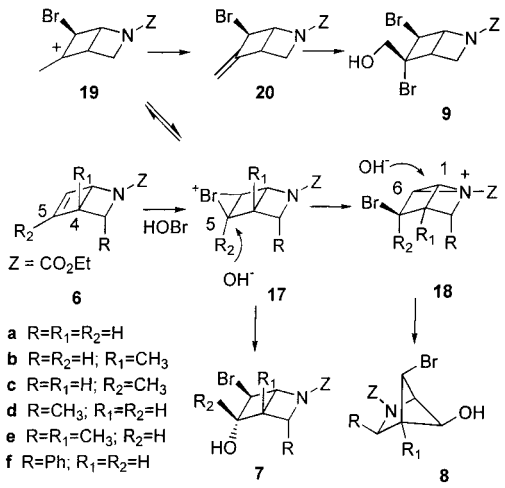


(methyl syn to the higher priority bridge) follows from the rearrangement mechanism (see Scheme 3).

Reductive Debromination of Halohydrins. Tributyltin hydride in refluxing benzene was used to remove the bromine atoms from the unrearranged bromohydrins **7a**,**b** and **11a**;[2] yields of the resulting novel 2-azabicyclo[2.2.0]hexanols are shown in Table 2. Of special interest was the structural assignment to the unrearranged alcohol **13b** (entry 2), which confirmed the stereochemical assignment of bromohydrin **7b** (Table 1, entry 2). The ^{1}H NMR spectrum of alcohol **13b** had coupling of the exo H_6 proton with H_1 ($J_{1,6exo}$ = 4.5 Hz) and with exo proton H_5 (J = 9.5 Hz), consistent with an endo assignment of its 5-hydroxyl group.

(10) Palumbo, G.; Ferreri, C.; Caputo, R. *Tetrahedron Lett.* **1983**, *24*, 1307.

Scheme 2



Scheme 3

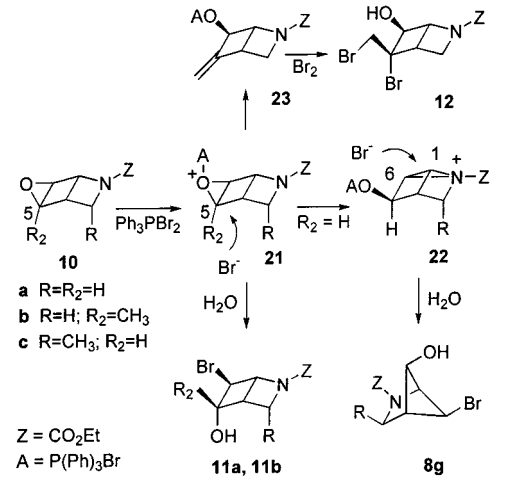
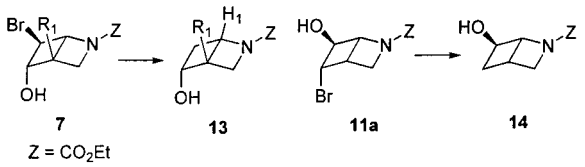


Table 2. Synthesis of 2-Azabicyclo[2.2.0]hexanols by Bu_3SnH Debromination of Bromohydrins



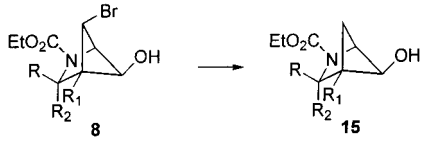
entry	bromohydrin	substituent R_1	product alcohol (Br = H)	yield (%)
1	**7a**	H	**13a**	73[a]
2	**7b**	CH_3	**13b**	53
3	**11a**	-	**14**	71

[a] See ref 2.

Yields in the reductive debromination reactions of the rearranged bromohydrins **8a**,**b** and **8d**−**g** to give alcohols **15** are shown in Table 3. Note that alcohols **8d** (entry 3) and **8g** (entry 6) have stereoisomeric 3-methyl groups.

Oxidative Hydroboration of 2-Azabicyclo[2.2.0]-hex-5-ene 6a. Addition of borane in THF to alkene **6a** followed by 30% HOOH in NaOH afforded low yields of a mixture of 6-*exo*-alcohol **14** (9%) and 5-exo alcohol **16** (5%) (eq 7). The structure of the 5-*exo*-alcohol **16** was based upon the identical couplings of exo proton H_6 at δ 2.27 with both H_1 and H_{5endo} (J = 5.1 Hz). A coupling J

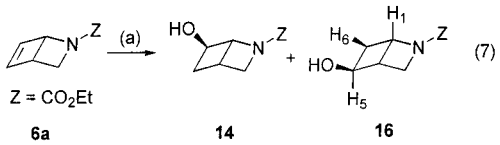
Table 3. Synthesis of 2-Azabicyclo[2.1.1]hexanols by Bu_3SnH Debromination of Bromohydrins



		substituents				
entry	bromohydrin	R	R_1	R_2	product alcohol	yield (%)
1	**8a**	H	H	H	**15a**	63[a]
2	**8b**	H	CH_3	H	**15b**	92
3	**8d**	CH_3	H	H	**15d**	50
4	**8e**	CH_3	CH_3	H	**15e**	81
5	**8f**	Ph	H	H	**15f**	92
6	**8g**	H	H	CH_3	**15g**	91

[a] See ref 2.

= 9.5 Hz is found between the exo protons H_6 and H_{5exo} in the isomeric 5-*endo*-hydroxyl compound **13a** (Table 2).



(a) B_2H_6, then HOOH, NaOH

Mechanistic Discussion. **Brominations.** Explanations for the formation of bromohydrins **7** and **8** from azabicyclo[2.2.0]hex-5-enes **6** shown in Table 1 are depicted in Scheme 2.[2] Addition of bromine to the open exo face of olefin **6a** affords bromonium ion **17a**. Selective attack of hydroxide at C_5 on the endo face of **17a** remote from the *N*-ethoxycarbonyl group provides mainly unrearranged bromohydrin **7a** (Table 1, entry 1). Competitively, participation by nitrogen can lead to the formation of aziridinium ion **18a**. Regioselective attack of hydroxide ion on intermediate **18a**, at the C_1 position farthest from the bromine at C_5, gives the minor rearranged bromohydrin **8a**.

Introduction of a methyl substituent at C_4 on the top face of alkene **6b** (Table 1, entry 2) results in a decrease in the amount of unrearranged bromohydrin **7b** (10%) so that it is a minor product and an increase in the amount of rearranged bromohydrin **8b** (44%). Relief of strain between the 4-methyl substituent and the *exo*-bromonium ion bridge in intermediate **17b** may drive rearrangement to the aziridinium ion **18b**, the precursor of the rearrangement product **8b**.

A methyl group attached to the alkene at C_5 (Table 1, entry 3) should stabilize intermediate **17c**, or perhaps its related tertiary carbocation **19**. Rearrangement of the methyl-substituted ion **17c** to aziridinium ion **18c** is noncompetitive. Addition of hydroxide ion to the endo face of intermediate **17c** should be disfavored because of steric crowding; however, attack of hydroxide from the endo face of intermediate **19** to give bromohydrin **7c** is reasonable if the exo bromine at C_6 hinders attack from the top face. The minor dibromohydrin **9** can be formed from the allylic bromide **20** by addition of bromine to the *endo* face, anti to the 6-bromo substituent, and attack of hydroxide at the terminal primary carbon. Attack at the less hindered primary carbon to give alcohol **9** is reasonable since the endo face at C_6 is quite crowded.

Of greater synthetic significance is the presence of the 3-*endo*-methyl or 3-*endo*-phenyl substituent in alkenes **6d**−**f** (Table 1, entries 4−6). The 3-*endo* substituents block hydroxide ion attack on the endo C_5 position of bromonium ions **17d**−**f**. Attack of hydroxide ion on aziridinium ions **18d**−**f** occurs to give only rearranged bromohydrins **8d**−**f**.

Epoxide Ring Openings. The mechanistic rationale for electrophilic ring opening of the epoxides **10** is shown in Scheme 3. Activation of the epoxide by coordination to a Lewis acid species affords intermediate **21**. In the absence of substituents at C_3 and C_5, bromide ion attacks intermediate **21a** at C_5, remote from the *N*-ethoxycarbonyl group, to give bromohydrin **11a**. If a methyl substituent is at C_5, bromide can attack intermediate **21b** to give bromohydrin **11b**, or ring opening can occur with loss of a proton to give alkene **23**. Formation of a bromonium ion on the *endo* face of **23** followed by bromide attack at the sterically accessible terminal position affords dibromo alcohol **12**. If an *endo* substituent is present at C_3, as in **21c**, bromide ion cannot approach the *endo* face at C_5. Thus, the ring nitrogen participates and causes epoxide ring opening of **21c** to form the aziridinium ion **22c**. Nucleophilic attack by bromide ion at C_1 of ion **22c** affords the rearranged bromohydrin **8g**.

Conclusions

It has been shown that the readily available N-(alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene ring system **6** can serve as the precursor of 5-hydroxy- and 6-hydroxy-2-azabicyclo[2.2.0]hexanes **13** and **14**, as well as rearranged 5-hydroxy-2-azabicyclo[2.1.1]hexanes **15**, via reductive debromination of regioselectively and stereoselectively formed precursor bromohydrins. Reactions of the substrate 2-azabicyclo[2.2.0]alkenes **6** can be somewhat fine-tuned by the presence of C_5-substituents, which block rearrangements, and 3-*endo* substituents, which facilitate rearrangement to novel 3-substituted-2-azabicyclo-[2.1.1]hexane bromohydrins **8**. The synthetic methods described for bromohydrin formation have potential utility for the stereocontrolled synthesis of more highly functionalized azabicyclohexanes, derivable by functional group variation in substrate alkenes **6** and modification of halogen and hydroxyl moieties.

Experimental Procedures[9]

The preparations of *N*-(ethoxycarbonyl)-1,2-dihydropyridines **5a**−**f** and *N*-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes **6a**−**f** have been described,[2,8,9] For purposes of nomenclature, 3-exo orientation on 2-azabicyclo[2.1.1]-hexanes **8**, **13**, and **16** refers to the 3-substituent oriented toward the bridge containing the lower priority attached 5- or 6-substituent. As a consequence of nomenclature, the stereochemistry of a C_3 group anti to the hydroxyl substituted bridge and syn to the bromine containing bridge changes from 3-endo to 3-exo upon removal of the bromine atom.

General Procedure for Addition of HOBr to *N*-(Ethoxycarbonyl)-2-azabicyclo[2.2.0]hexenes 6b−f. The previously described procedure[2] was followed in which NBS (3 mmol) was added in small portions, so that the temperature never exceeded 0 °C, to a solution of alkene **6** (1 mmol) in DMSO (6 mL) and water (3 mL). The solution was then stirred for 12−16 h at 25 °C, diluted with water (20 mL), and extracted with ether (6 × 10 mL). The combined extracts were washed with water (20 mL) and dried over $MgSO_4$, the solvent was removed in vacuo, and flash chromatography of the residue if necessary was performed on silica gel (2:1 ether/hexane).

Preparation of *N*-(Ethoxycarbonyl)-6-*exo*-bromo-5-*endo*-hydroxy-4-methyl-2-aza-bicyclo[2.2.0]hexane (7b) and *N*-(Ethoxycarbonyl)-5-*anti*-bromo-6-*anti*-hydroxy-4-methyl-2-azabicyclo[2.1.1]hexane (8b). From 4-methyl-2-azabicyclo[2.2.0]hexene **6b** (100 mg, 0.6 mmol) and NBS (320 mg, 1.8 mmol) in 2:1 DMSO/water (9 mL) there was obtained according to the general procedure followed by preparative TLC (2:1 hexane/ether and four exposures to the solvent chamber) an 81:19 ratio of 16 mg (10%) of unrearranged bromohydrin **7b** at $R_f = 0.58$ (3:1 ether/hexane): ^{1}H NMR δ 1.25 (t, $J = 7.2$ Hz, 3H), 1.46 (s, 3H), 2.91 (br, 1H, OH), 3.69 (d, $J = 9$ Hz, 1H), 4.13 (q, $J = 7.2$ Hz, 2H), 4.13 (m, 2H), 4.37 (s, 1H), 4.48 (d, $J = 9$ Hz, 1H); ^{13}C NMR δ14.6, 20.9, 42.9, 49.3, 53.0, 61.3, 66.9, 82.0, 156.3; HRMS (FAB) *m*/*z* 264.0230, 266.0218, calcd for C_9H_{15}79/81$BrNO_3$ (MH^+) 264.0235, 266.0215. There also was obtained 70 mg (44%) of rearranged bromohydrin **8b** at $R_f = 0.52$: ^{1}H NMR δ 1.25 (t, $J = 7.2$ Hz, 3H), 1.25 (s, 3H), 3.25 (bs, 1H, OH), 3.39 (d, $J = 9.0$ Hz, 1H), 3.45 (d, $J = 9.0$ Hz, 1H), 4.04 (s, 2H), 4.14 (q, $J = 7.2$ Hz, 2H), 4.36 (s, 1H); ^{13}C NMR δ 10.2, 14.6, 52.8, 53.6, 57.2, 61.6, 63.9, 83.5, 155.2; HRMS (FAB) *m*/*z* 264.0235, 266.0222, calcd for $C_9H_{15}{}^{79/81}BrNO_3$ (MH^+) 264.0235, 266.0215.

Preparation of *N*-(Ethoxycarbonyl)-6-*exo*-bromo-6-*endo*-hydroxy-5-*exo*-methyl-2-azabicyclo[2.2.0]hexane (7c) and *N*-(Ethoxycarbonyl)-5-*exo*-6-*exo*-dibromo-7-*endo*-hydroxymethyl-2-azabicyclo[2.2.0]hexane (9). From 5-methyl-2-azabicyclo[2.2.0]hexene **6c** (100 mg, 0.60 mmol) and NBS (320 mg, 1.8 mmol) in 2:1 DMSO/water (9 mL) there was obtained according to the general procedure following flash chromatography 120 mg (76%) bromohydrin **8c** at $R_f = 0.55$ (4:1 ether/hexane): ^{1}H NMR (70 °C) δ 1.22 (t, $J = 7.2$ Hz, 3H), 1.44 (s, 3H), 2.38 (bs, 1H, OH), 2.96 (ddd, $J = 7.5$, 5.1, 3.3 Hz, 1H), 4.03 (dd, $J = 9.6$, 7.5 Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 4.24 (d, $J = 5.1$ Hz, 1H), 4.40 (dd, $J = 9.6$, 3.3 Hz, 1H), 4.48 (s, 1H); ^{13}C NMR (70 °C) δ 14.6, 27.7, 41.6, 49.2, 57.8, 61.4, 62.6, 73.7, 155.9; HRMS (FAB) *m*/*z* 264.0225, 266.0219, calcd for C_9H_{15}79/81$BrNO_3$ (MH^+) 264.0235, 266.0215. There also was obtained 30 mg (19%) of dibromo alcohol **9** at $R_f = 0.61$ (4:1 ether/hexane): ^{1}H NMR δ 1.27 (t, $J = 7.2$ Hz, 3H), 2.29 (t, 6.6 Hz, 1H, OH), 3.42 (ddd, $J = 7.5$, 4.8, 3.3 Hz, 1H), 3.96 (dd, $J = 12.6$, 6.6 Hz, 1H), 4.02 (dd, $J = 12.6$, 6.6 Hz, 1H), 4.16 (q, $J = 7.2$ Hz, 2H), 4.34 (dd, $J = 9.6$, 7.5 Hz, 1H), 4.35 (dd, $J = 9.6$, 3.3 Hz, 1H), 4.58 (d, $J = 4.8$ Hz, 1H), 4.93 (s, 1H); ^{13}C NMR δ 14.6, 40.2, 54.0, 55.0, 56.0, 61.6, 66.3, 69.7, 155.1; HRMS (FAB) *m*/*z* 341.9339, 343.9317, 345.9306, calcd for $C_9H_{14}{}^{79/79,79/81,81/81}BrNO_3$ (MH^+) 341.9340, 343.9320, 345.9306.

Preparation of *N*-(Ethoxycarbonyl)-5-*anti*-bromo-6-*anti*-hydroxy-3-*endo*-methyl-2-azabicyclo[2.1.1]hexane (8d). From 3-*endo*-methyl-2-azabicyclo[2.2.0]hexene **6d** (106 mg, 0.63 mmol) and NBS (339 mg, 1.9 mmol) in 2:1 DMSO/water (9 mL) there was obtained according to the general procedure 142 mg (85%) of rearranged bromohydrin **8d** at $R_f = 0.48$ (3:1 ether/hexane): ^{1}H NMR δ 1.25 (t, $J = 7.2$ Hz, 3H), 1.36 (d, $J = 6.3$ Hz, 3H), 2.71 (d, $J = 7.5$ Hz, 1H), 3.30 (bs, 1H, OH), 3.91 (q, $J = 6.3$ Hz, 1H), 4.14 (d, $J = 7.5$ Hz, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 4.30 (d, $J = 7.5$ Hz, 1H), 4.36 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 14.5, 18.1, 49.7, 54.9, 56.4, 61.4, 66.6, 86.3, 155.4; HRMS (EI) *m*/*z* 262.0090, 264.0137, calcd for $C_9H_{13}{}^{79/81}BrNO_3$ (MH^+) 262.0079, 264.0059.

Preparation of *N*-(Ethoxycarbonyl)-5-*anti*-bromo-6-*anti*-hydroxy-3-*endo*,4-di-methyl-2-azabicyclo[2.1.1]-hexane (8e). From 3-*endo*-4-dimethyl-2-azabicyclo[2.2.0]-hexene **6e** (180 mg, 0.99 mmol) and NBS (536 mg, 2.98 mmol) in 2:1 DMSO/water (9 mL) there was obtained according to the general procedure 165 mg (60%) of rearranged dibromide **8e** at $R_f = 0.42$ (3:1 ether/hexane): ^{1}H NMR δ 1.15 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.28 (d, $J = 6.3$ Hz, 3H), 2.92 (bs, 1H, OH), 3.70 (q, $J = 6.3$ Hz, 3H), 3.91 (d, $J = 7.5$ Hz, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 4.23 (d, $J = 7.5$ Hz, 1H), 4.38 (s, 1H); ^{13}C NMR δ 14.5, 15.5, 54.5, 56.0, 59.5, 61.3, 64.1, 86.8, 155.5; HRMS (EI) *m*/*z* 198.1127, calcd for $C_{10}H_{16}NO_3$ ($M^+ - Br$), 198.1130.

Preparation of *N*-(Ethoxycarbonyl)-5-*anti*-bromo-6-*anti*-hydroxy-3-*endo*-phenyl-2-azabicyclo[2.1.1]hexane (8f). From 3-*endo*-phenyl-2-azabicyclo[2.2.0]hexene **6f** (90 mg, 0.39 mmol) and NBS (267 mg, 1.5 mmol) in 2:1 DMSO/water (4.5 mL) there was obtained according to the general procedure a mixture, which upon column chromatography gave 77.6 mg (61%) of rearranged bromohydrin **8f** ($R_f = 0.56$ (5:1 ether/hexane): ^{1}H NMR δ 1.26 (t, 3H), 3.05 (d, $J = 7.2$ Hz, 1H), 3.50 (br, 1H), 4.19 (m, 3H), 4.29 (d, $J = 7.5$ Hz, 1H), 4.53 (d, $J = 7.2$ Hz, 1H), 5.03 (s, 1H), 7.35 (m, 5H); ^{13}C NMR δ 14.5, 48.5, 55.6, 61.9, 63.0, 66.6, 86.0, 126.1, 127.5, 128.5, 138.2, 156.3; HRMS (FAB) *m*/*z* 326.0375/328.0351, calcd for $C_{14}H_{17}{}^{79/81}BrNO_3$ (M + 1) 326.0386/328.0366.

Preparation of *N*-(Ethoxycarbonyl)-3-aza-7-oxatricyclo-[4.1.0.0^{2,5}]heptanes 10. Similar to the procedure described by Tsuchiya,[8c] a solution of the alkene **6a**, **6c**, or **6d** in CH_2Cl_2 (10 mL) was added dropwise to a solution of *m*-CPBA (2 mol eq) in CH_2Cl_2 (10 mL) at room temperature. After stirring for 30−36 h, the solution was diluted with CH_2Cl_2 (30 mL) and successively washed with satd $NaHCO_3$ (6 × 10 mL), satd NaCl (10 mL), and water (10 mL) and dried over $MgSO_4$, and solvent was removed in vacuo to give epoxides **10** as oils. Further purification could be effected by flash column chromatography on alumina (3:1 hexane/ether).

***N*-(Ethoxycarbonyl)-3-aza-7-oxatricyclo[4.1.0.0^{2,5}]-heptane (10a).** From 2-azabicyclo[2.2.0]hex-5-ene **6a** (300 mg, 1.96 mmol) and *m*-CPBA (676 mg, 3.92 mmol) there was obtained according to the general procedure 252 mg (76%) of oily epoxide **10** at $R_f = 0.31$ (1:1 hexane/ether): ^{1}H NMR (80 °C) δ 1.20 (t, $J = 7.0.2$ Hz, 3H), 2.88 (m, 1H), 3.82 (dd, $J = 9.3$, 1.0 Hz, 1H), 3.97 (m, 1H), 4.00 (m, 1H), 4.07 (q, $J = 7.2$ Hz, 2H), 4.14 (bs, 1H), 4.38 (bs, 1H); ^{13}C NMR δ 15.1, 40.3, 48.6, 56.0, 56.3, 61.6, 68.0, 156.7; HRMS (FAB) *m*/*z* 170.0818, calcd for $C_8H_{12}NO_3$ (MH^+), 170.0817.

***N*-(Ethoxycarbonyl)-6-*endo*-methyl-3-aza-7-oxatricyclo-[4.1.0.0^{2,5}]heptane (10b).** From 5-azabicyclo[2.2.0]hex-5-ene **6c** (133 mg, 0.80 mmol) and *m*-CPBA (277 mg, 1.60 mmol) there was obtained according to the general procedure 145 mg (97%) of oily epoxide **10b** at $R_f = 0.35$ (1:1 hexane/ether): ^{1}H NMR δ 1.17 (t, $J = 7.2$ Hz, 3H), 1.51 (s, 3H), 2.83 (m, 1H), 3.77 (d, $J = 9.1$ Hz, 1H), 3.97 (m, 1H), 4.04 (q, $J = 7.2$ Hz, 2H), 4.04 (m 1H), 4.26 (bs, 1H); ^{13}C NMR δ 12.0, 14.6, 41.6, 48.2, 60.9, 61.0, 64.0, 65.5, 156.1; HRMS (FAB) *m*/*z* 184.0972, calcd for $C_9H_{14}NO_3$ (MH^+), 184.0974. The crude epoxide **10b** was sufficiently pure for further reaction. Column chromatography afforded 69 mg (47%) of pure epoxide **10b**, which was shown to decompose upon exposure to both neutral alumina and silica gel.

***N*-(Ethoxycarbonyl)-4-*endo*-methyl-3-aza-7-oxatricyclo-[4.1.0.0^{2,5}]heptane (10c).** From 3-*endo*-methyl-2-azabicyclo-[2.2.0]hex-5-ene **6d** (335 mg, 2.0 mmol) and *m*-CPBA (518 mg, 3.0 mmol) there was obtained according to the general procedure following flash column chromatography (3:1 hexane/ether, silica gel) 283 mg (77%) of a clear oil ($R_f = 0.39$, 1:1 hexane/ether); ^{1}H NMR (70 °C) δ 1.25 (t, $J = 7.2$ Hz, 3H), 1.42 (d, $J = 6.6$ Hz, 3H), 2.86 (ddd, $J = 7.2$, 3.9, 2.4 Hz, 1H), 3.89 (d, $J = 4.5$, 1.8 Hz, 1H), 4.02 (q, $J = 7.2$ Hz, 2H), 4.08 (dd, $J = 3.9$, 1.8 Hz, 1H), 4.29 (dd, $J = 4.5$, 2.4 Hz, 1H), 4.36 (dq, $J = 7.2$, 6.6 Hz, 1H); ^{13}C NMR δ 14.5, 17.0, 44.5, 53.6, 56.8 (2C), 60.3, 65.7, 155.8; HRMS (FAB) *m*/*z* 184.0970, calcd for C_9H_{14}-NO_3 (MH^+), 184.0974.

General Procedure for Rearrangement of Epoxides 10 to Bromohydrins. Preparation of *N*-(Ethoxycarbonyl)-5-*endo*-bromo-6-*exo*-hydroxy-2-azabicyclo[2.2.0]-hexane (11a). According to the procedure of Palumbo[10] a solution of bromine (1.93 mmol) in CH_2Cl_2 (20 mL) was added to triphenylphosphine (212 mg, 1.93 mmol) as a solid with stirring. The epoxide **10a** (300 mg, 1.77 mmol) in CH_2Cl_2 (10 mL) was added, and the mixture was stirred 18 h under Ar. The reaction was quenched with 10% sodium thiosulfate, the layers were separated, the organic layer was extracted with water (15 mL) and dried over $MgSO_4$, and solvent was removed in vacuo to give a residue which upon silica gel chromatography (2:1 hexane/ether) afforded 297 mg (67%) of oily bromohydrin **11a** at $R_f = 0.24$ (1:1 hexane/ether): ^{1}H NMR (acetone-d_6, 70 °C) δ1.20 (t, $J = 7.2$ Hz, 3H), 3.22 (dddd, $J = 7.2$, 6.0, 4.2, 1.8 Hz, 1H), 4.07 (q, $J = 7.2$ Hz, 2H), 4.16 (dd, $J = 9.0$, 6.0 Hz, 1H), 4.25 (dd, $J = 9.0$, 1.8 Hz, 1H), 4.31 (d, $J = 4.2$ Hz,

1H), 4.40 (d, J = 5.4 Hz, 1H), 4.57 (dd, J = 7.2, 5.4 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 14.8, 32.9, 52.6, 52.7, 61.2, 68.0, 83.7, 155.7; HRMS (FAB) m/z 250.0073, 252.0059, calcd for $C_8H_{13}{}^{79/81}BrNO_3$ (MH^+), 250.0079, 252.0058.

***N*-(Ethoxycarbonyl)-5-*endo*-bromo-6-*exo*-hydroxy-5-*exo*-methyl-2-azabicyclo[2.2.0]hexane (11b) and *N*-(Ethoxycarbonyl)-5-*exo*-bromo-5-*endo*-bromomethyl-6-*exo*-hydroxy-2-azabicyclo[2.2.0]hexane (12).** From epoxide **10b** (178 mg, 0.97 mmol), triphenylphosphine (118 mg, 1.07 mmol), and bromine (171 mg, 1.07 mmol) after 20 min there was obtained according to the general procedure a mixture of products, which upon flash column chromatography (2:1 hexane/ether) afforded 50 mg (20%) of oily bromohydrin **11b** at R_f = 0.26; ^{1}H NMR δ 1.26 (t, J = 7.2 Hz, 3H), 1.85 (s, 3H), 2.82 (ddd, J = 7.5, 4.8, 3.6 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 4.25 (dd, J = 9.9, 7.5 Hz, 1H), 4.25 (bs, OH), 4.34 (d, J = 4.8 Hz, 1H), 4.37 (dd, J = 9.9, 3.6 Hz, 1H), 4.72 (s, 1H); ^{13}C NMR δ 15.3, 26.7, 41.4, 55.9, 62.3, 65.1, 66.7, 85.1, 156.8; HRMS (FAB) m/z 264.0234, 266.0218, calcd for C_9H_{15}79/81$BrNO_3$ (MH^+), 264.0235, 266.0215. There was also obtained 46 mg (14%) of an oily dibromohydrin **12** at R_f = 0.34 (1:1 hexane/ether): ^{1}H NMR δ 1.32 (t, J = 7.2 Hz, 3H), 3.18 (m, 1H), 3.98 (d, 11.7 Hz, 1H), 4.05 (d, J = 11.7 Hz, 1H), 4.19 (br, OH), 4.19 (q, J = 7.2 Hz, 2H), 4.38 (m, 2H), 4.46 (d, J = 4.8 Hz, 1H), 4.88 (d, $J_{6,OH}$ = 5.1 Hz, 1H); HRMS (FAB) m/z 341.9301, 343.9328, 345.9299, calcd for $C_9H_{14}{}^{79/79,79/81,81/81}BrNO_3$ (MH^+), 341.9340, 343.9320, 345.9357.

***N*-(Ethoxycarbonyl)-5-*anti*-bromo-6-*anti*-hydroxy-3-*exo*-methyl-2-azabicyclo[2.1.1]hexane (8g).** From 3-*endo*-methyl epoxide **10c** (100 mg, 0.54 mmol), triphenylphosphine (65 mg, 0.59 mmol), and bromine (94 mg, 0.59 mmol) after 18 h there was obtained according to the general procedure after chromatography (silica gel, 1:1 ether/hexane) 93 mg (65%) of a clear oil, R_f = 0.26 (1:1 hexane/ether): ^{1}H NMR δ 1.22, (t, J = 7.2 Hz, 3H), 1.34 (d, J = 6.6 Hz, 3H), 2.70 (d, J = 7.2 Hz, 1H), 3.57 (bs, OH), 3.93, (d, J = 6.6 Hz, 1H), 3.98 (d, J = 7.2 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 4.35 (d, J = 7.2 Hz, 1H), 4.41 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 14.5, 17.5, 53.3, 54.5, 56.9, 61.5, 66.4, 81.9, 156.0; HRMS (FAB) m/z 264.0227, 266.0214, calcd for $C_9H_{15}{}^{79/81}BrNO_3$ (MH^+), 264.0235, 266.0215.

General Procedure for Debrominations of 5-Bromo-2-azabicyclo[2.2.0]- and [2.1.1]hexanols 7, 8, and 11. Preparation of Alcohols 13−15. The previously described procedure[2] utilized for bromohydrin **8a** was followed in which the bromohydrin (0.56 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN) (90 mg, 0.54 mmol) were dissolved in benzene (10 mL), the system was purged with argon for 15 min, tributyltin hydride (454 μL, 491 mg, 1.69 mmol) was added through a rubber septum, and the resulting solution was heated to 80 °C for 2 h. The reaction mixture was cooled to room temperature, and the benzene was removed in vacuo to give a residue that upon chromatography (10:1 hexane/ether) gave the desired alcohols **13**−**15**.

N-(Ethoxycarbonyl)-5-*endo*-hydroxy-2-azabicyclo[2.2.0]-hexane (13a). Reduction of bromohydrin **7a** (89 mg, 0.36 mmol) with tributyltin hydride (145 μL, 157 mg, 0.54 mmol) according to the general procedure afforded after column chromatography (2:1 ether/hexane, silica gel) 45 mg (73%) of alcohol **13a** as a clear oil, R_f = 0.18 (3:1 ether/hexane); ^{1}H NMR δ 1.17 (t, J = 7.2 Hz, 3H), 2.2 (dd, J = 14.4, 5.7 Hz, 1H), 2.78 (dddd, J = 14.4, 9.0, 4.5, 1.5 Hz, 1H), 3.11 (m, 1H), 3.40 (br, OH), 4.04 (q, J = 7.2 Hz, 2H), 4.04 (m, 1H), 4.23 (t, J = 4.5 Hz, 1H), 4.48 (dd, J = 9.3, 2.7 Hz, 1H), 4.53 (m, 1H); ^{13}C NMR δ 14.7, 37.2, 39.5, 47.8, 56.0, 60.8, 63.9, 155.8; HRMS (FAB) m/z 172.0976, calcd for $C_8H_{14}NO_3$ (MH^+), 172.0974.

***N*-(Ethoxycarbonyl)-5-*endo*-hydroxy-4-methyl-2-azabicyclo[2.2.0]hexane (13b) and *N*-(Ethoxycarbonyl)-5-*anti*-hydroxy-4-methyl-2-azabicyclo[2.1.1]hexane (15b).** Reduction of 36:64 mixture of bromohydrins **7b** and **8b** (184 mg, 0.70 mmol) with tributyltin hydride (282 μL, 306 mg, 1.05 mmol) according to the general procedure afforded after column chromatography (2:1 ether/hexane, silica gel) 25 mg (53%) of alcohol **14b** as a clear oil (R_f = 0.21, 3:1 ether/hexane); ^{1}H NMR δ 1.22 (t, J = 7.0 Hz, 3H), 1.29 (s, 3H), 2.05 (dd, J = 14.5, 5.5 Hz, 1H), 2.74 (ddd, J = 14.5, 9.5, 4.5 Hz, 1H), 2.87 (br, OH), 3.68 (d, J = 8.5 Hz, 1H), 3.96 (d, J = 4.5 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 4.18 (dd, J = 9.5, 5.5 Hz, 1H), 4.56 (d, J = 8.5 Hz, 1H); ^{13}C NMR δ 15.4, 20.9, 37.3, 45.0, 54.4, 59.6, 61.6, 71.3, 156.8; HRMS (FAB) m/z 186.1126, calcd for $C_9H_{16}NO_3$ (MH^+), 186.1130. There was also obtained 76 mg (92%) of alcohol **15b** as a clear oil (R_f = 0.38, 3:1 ether/hexane); ^{1}H NMR δ 1.22 (t, J = 7.0 Hz, 3H), 1.29 (s, 3H), 2.05 (dd, J = 14.5, 5.5 Hz, 1H), 2.74 (ddd, J = 14.5, 9.5, 4.5 Hz, 1H), 2.87 (br, OH), 3.68 (d, J = 8.5 Hz, 1H), 3.96 (d, J = 4.5 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 4.18 (dd, J = 9.5, 5.5 Hz, 1H), 4.56 (d, J = 8.5 Hz); ^{13}C NMR δ 15.4, 20.9, 37.3, 45.0, 54.4, 59,6, 61.6, 71.3, 156.8; HRMS (FAB) m/z 186.1126, calcd for $C_9H_{16}NO_3$ (MH^+), 186.1130.

***N*-(Ethoxycarbonyl)-6-*exo*-hydroxy-2-azabicyclo[2.2.0]-hexane (14).** Reduction of bromohydrin **11a** (443 mg, 1.77 mmol) with tributyltin hydride (726 μL, 786 mg, 2.7 mmol) according to the general procedure afforded after column chromatography (3:1 ether/hexane, silica gel) 215 mg (71%) of alcohol **15** (R_f = 0.28, 3:1 ether/hexane); ^{1}H NMR δ 1.18 (t, J = 7.2 Hz, 3H), 2.25 (m, 1H), 2.51 (m, 1H), 2.82 (m, 1H), 3.81 (m, 1H), 4.05 (q, J = 7.2 Hz, 2H), 4.19 (dd, J = 8.7, 6.3 Hz, 1H), 4.31 (d, 4.5 Hz, 1H), 4.40 (m, 1H); ^{13}C NMR δ 15.4, 27.7, 37.3, 57.2, 61.6, 70.7, 73.4, 156.6; HRMS (FAB) m/z 172.0975, calcd for $C_8H_{14}NO_3$ (MH^+), 172.0974.

***N*-(Ethoxycarbonyl)-5-*anti*-hydroxy-3-*exo*-methyl-2-azabicyclo[2.1.1]hexane (15d).** Reduction of bromohydrin **8d** (169 mg, 0.64 mmol) with tributyltin hydride (258 μL, 279 mg, 0.96 mmol) according to the general procedure afforded after column chromatography (3:1 ether/hexane, silica gel) 59 mg (50%) of alcohol **15d** (R_f = 0.25, 3:1 ether/hexane); ^{1}H NMR δ 1.24 (t, J = 6.9 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H), 1.81 (dd, J = 8.1, 7.5 Hz, 1H), 2.41 (dd, J = 7.5, 3.3 Hz, 1H), 2.79 (ddd, J = 8.1, 3.3, 2.7 Hz), 3.11 (s, OH), 3.78 (q, J = 6.0 Hz, 1H), 4.00 (d, J = 7.5 Hz, 1H), 4.12 (q, J = 6.9 Hz, 2H), 4.12 (dd, J = 7.5, 2.7 Hz, 1H); ^{13}C NMR δ 14.6, 17.5, 33.0, 49.3, 54.5, 60.8, 63.8, 82.3, 156.4; HRMS (EI) m/z 185.1042, calcd for $C_9H_{15}NO_3$, 185.1052.

***N*-(Ethoxycarbonyl)-5-*anti*-hydroxy-3-*exo*-4-dimethyl-2-azabicyclo[2.1.1]hexane (15e).** Reduction of bromohydrin **8e** (130 mg, 0.38 mmol) with tributyltin hydride (153 μL, 166 mg, 0.57 mmol) according to the general procedure afforded after column chromatography (3:1 ether/hexane, silica gel) 62 mg (81%) of alcohol **15e** (R_f = 0.28, 3:1 ether/hexane); ^{1}H NMR δ 1.04 (s, 3H), 1.23 (d, J = 6.3 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.74 (dd, J = 7.8, 6.9 Hz, 1H), 2.05 (br, OH), 2.40 (dd, J = 7.8, 1.8 Hz, 1H), 3.47 (dq, J = 6.3 Hz, 1H), 3.78 (d, J = 6.9 Hz, 1H), 4.10 (d, J = 1.8 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H); ^{13}C NMR δ 10.7, 14.5, 15.1, 35.8, 53.2, 58.2, 60.6, 61.1, 82.7, 156.3; HRMS (EI) m/z 199.1212, calcd for $C_{10}H_{17}NO_3$, 199.1208.

***N*-(Ethoxycarbonyl)-5-*anti*-hydroxy-3-*exo*-phenyl-2-azabicyclo[2.1.1]hexane (15f).** Reduction of bromohydrin **8f** (120 mg, 0.37 mmol) with tributyltin hydride (280 μL, 302 mg, 1.0 mmol) according to the general procedure afforded after column chromatography (2:1 ether/hexane, silica gel) 84 mg (92%) of alcohol **15f** (R_f = 0.13, 2:1 ether/hexane); ^{1}H NMR δ 1.12 (br, 3H), 1.77 (dd, J = 5.7, 7.5 Hz, 1H), 2.71 (d, J = 7.5 Hz, 1H), 2.72 (d, J = 6.6 Hz, 1H), 3.77 (br, 1H), 4.12 (br, 2H), 4.17 (d, J = 5.7 Hz, 1H), 4.30 (d, J = 6.6 Hz, 1H), 4.89 (s, 1H), 7.22−7.36 (m, 5H); ^{13}C NMR δ 14.6, 31.8/32.4, 50.5, 61.3, 61.5, 63.8, 82.0, 126.2, 126.9, 128.1, 139.6, 157.3; HRMS (FAB) m/z 270.1094, calcd for $C_{14}H_{17}NO_3Na$ (MNa^+), 270.1126.

***N*-(Ethoxycarbonyl)-5-*anti*-hydroxy-3-*endo*-methyl-2-azabicyclo[2.1.1]hexane (15g).** Reduction of bromohydrin **8g** (45 mg, 0.17 mmol) with tributyltin hydride (69 μL, 74 mg, 0.26 mmol) according to the general procedure afforded after washing with sat. KF (1 × 10 mL) to remove tin halide and column chromatography (2:1 ether/hexane, silica gel) 29 mg (91%) of alcohol **15g** (R_f = 0.32, 2:1 ether/hexane); ^{1}H NMR δ 1.31 (t, J = 7.2 Hz, 3H), 1.38 (d, J = 6.3 Hz, 3H), 1.62 (t, J = 7.2 Hz, 1H), 2.49 (dd, J = 7.5, 3.0 Hz, 1H), 2.6 (s, 1H), 2.93 (d, J = 7.2 Hz, 1H), 3.85 (q, J = 6.3 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.23 (d, J = 7.5 Hz, 1H), 4.37 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 14.7, 17.3, 38.9, 49.3, 56.1, 60.9, 64.3, 78.2, 156.6; HRMS (FAB) m/z 186.1125, calcd for $C_9H_{16}NO_3$ (MH^+) 186.1130.

Oxidative Hydroboration of Alkene 6a. *N*-(Ethoxycarbonyl)-6-*exo*-hydroxy-2-azabicyclo[2.2.0]hexane (14) and *N*-(Ethoxycarbonyl)-5-*exo*-hydroxy-2-azabicyclo[2.2.0]-hexane (16). To a solution of alkene **6a** (500 mg, 3.26 mmol) in THF (10 mL) at 0 °C under argon there was added a solution of 1 M BH_3 in THF (4 mL, 3.52 mmol) over 2 min. After being stirred for 1 h, the reaction was quenched with water (1 mL), and 3 N NaOH (1 mL) followed by 30% HOOH (1 mL) was added slowly. After stirring for 1 h, water (5 mL) was added, the solution was extracted with ether and dried over $MgSO_4$, and solvent was removed in vacuo to give a mixture of oils, which upon column chromatography (2:1 hexane/ether) gave 49 mg (9%) of alcohol **14** (R_f = 0.21, 3:1 ether/hexane) described above. There also was obtained 28 mg (5%) of alcohol **16** (R_f = 0.13 (3:1 ether/hexane); ^{1}H NMR δ 1.17 (t, J = 7.2 Hz, 3H), 2.27 (ddd, J = 13.8, 5.1, 5.1 Hz, 1H), 2.74 (m, 2H), 2.92 (br, OH), 3.84 (dd J = 9.0, 3.1 Hz, 1H), 4.04 (q, J = 7.2 Hz, 2H), 4.16 (dd, J = 9.0, 7.5 Hz, 1H), 4.50 (m, 2H); ^{13}C NMR δ 15.4, 41.7, 41.9, 54.2, 59.4, 61.6, 73.8, 156.2; HRMS (FAB) m/z (MH^+) 172.0973, calcd for $C_8H_{14}NO_3$, 172.0974.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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